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The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine. A cross-over study with extensive and quinidine-induced poor metabolizers

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Aims Dihydrocodeine is metabolized to dihydromorphine via the isoenzyme cytochrome P450 2D6, whose activity is determined by genetic polymorphism. The importance of the dihydromorphine metabolites for analgesia in poor metabolizers is unclear. The aim of this study was to assess the importance of the dihydromorphine metabolites of dihydrocodeine in analgesia by investigating the effects of dihydrocodeine on somatic and visceral pain thresholds in extensive and quinidine-induced poor metabolizers.

Methods Eleven healthy subjects participated in a double-blind, randomized, placebo-controlled, four-way cross-over study comparing the effects of single doses of placebo and slow-release dihydrocodeine 60 mg with and without premedication with quinidine sulphate 50 mg on electrical, heat and rectal distension pain tolerance thresholds. Plasma concentrations and urinary excretion of dihydrocodeine and dihydromorphine were measured.

Results In quinidine-induced poor metabolizers the plasma concentrations of dihydromorphine were reduced between 3 and 4 fold from 1.5 h to 13.5 h after dosing ($P<0.005$) and urinary excretion of dihydromorphine in the first 12 h was decreased from 0.91% to 0.28% of the dihydrocodeine dose ($P<0.001$). Dihydrocodeine significantly raised the heat pain tolerance thresholds (at 3.3 h and 5 h postdosing, $P<0.05$) and the rectal distension defaecatory urge (at 3.3 h and 10 h postdosing, $P<0.02$) and pain tolerance thresholds (at 3.3 h and 5 h postdosing, $P<0.05$) compared with placebo. Premedication with quinidine did not change the effects of dihydrocodeine on pain thresholds, but decreased the effect of dihydrocodeine on defaecatory urge thresholds (at 1.5 h, 3.3 h and 10 h postdosing, $P<0.05$).

Conclusions In quinidine-induced poor metabolizers significant reduction in dihydromorphine metabolite production did not result in diminished analgesic effects of a single dose of dihydrocodeine. The metabolism of dihydrocodeine to dihydromorphine may therefore not be of clinical importance for analgesia. This conclusion must however, be confirmed with repeated dosing in patients with pain.

Keywords: antinociception, dihydrocodeine, dihydromorphine, metabolism, P450 2D6, pain, quinidine, somatic, visceral

Introduction

Dihydrocodeine has established analgesic efficacy and a parenteral potency of approximately one-sixth of morphine and equipotency to codeine [1–3]. It has been suggested that dihydrocodeine and codeine have little analgesic effect of their own, but rather function as prodrugs, with the main analgesic effect being attributable to their morphine metabolites [4–7]. The metabolic conversion to morphine and dihydromorphine from codeine and dihydrocodeine, respectively, is by *O*-demethylation via the isoenzyme cytochrome P450 2D6, the activity of which is determined by genetic polymorphism [8]. Approximately 5–10% of Caucasians and slightly more Asians are deficient in this pathway and can be classified as poor metabolizer phenotypes using debrisoquine, sparteine or dextrometorphan as marker substances [9]. Poor metabolizers will produce fewer active metabolites of *O*-demethylated analgesics, such as codeine and dihydrocodeine, and are therefore postulated to derive a lesser analgesic effect.

The aim of the present study was to assess the importance of the systemic morphine metabolites of dihydrocodeine for analgesia with somatic and visceral sensory and pain tests. For this purpose formation of the systemic morphine metabolites was blocked using quinidine premedication, which has been shown to chemically convert extensive metabolizers to poor metabolizers by interfering with *O*-demethylation [6, 10].

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Methods

Eleven male healthy volunteers of age 20–35 years were recruited for this double-blind, randomized, placebo-controlled, four-way cross-over study. All subjects gave their written informed consent and University of Berne Ethics Committee approval was gained for the study. Exclusion criteria were use of any medication or any illness within 4 weeks before the start of the study, previous gastroenterological or hepatological diseases, abnormal anorectal anatomy or sensitivity compared with our own clinical database, drug abuse, diabetes mellitus or neuropathies. They were tested for their cytochrome P450 2D6 metabolizer phenotype 1 week before the start of the study using debrisoquine 10 mg (Declinax®, Hoffmann-LaRoche, Basle, Switzerland) and measurement of debrisoquine and its 4-hydroxy-metabolite by gas chromatography in the following 8 h urine collection [11]. One poor metabolizer was excluded from the study and replaced. All subjects were instructed in detail concerning each of the test procedures and test runs were performed 1 week before the start of the study to ensure familiarization with the tests.

The study consisted of four randomized oral treatment arms: 1) placebo followed by placebo 2), quinidine sulphate 50 mg (University Hospital Pharmacy, Berne, Switzerland) followed by placebo 3), placebo followed by slow-release dihydrocodeine 60 mg (90 mg Dihydrocodeine continus®, Mundipharma Pharmaceuticals, Basle, Switzerland, corresponds to 60 mg dihydrocodeine base) or 4) quinidine sulphate 50 mg followed by slow-release dihydrocodeine 60 mg. The randomization list for the medication sequence was generated by computer programme. There was a washout period of at least 1 week between the study arms. The study days were completely standardized regarding the testing times and the meals, which were eaten at 12.15 h and 21.00 h. Two subjects were tested per study day, which began at 08.00 h and finished at 23.30 h. According to the randomization, either placebo or quinidine was taken at 08.00 h and followed by placebo or dihydrocodeine at 10.00 h. All subjects had an intravenous catheter with a replaceable stylet placed in a forearm vein for repeated withdrawal of blood samples for plasma concentration determination (at 0, 1.5, 3.3, 5, 10 and 13.5 h postdihydrocodeine dosing). The blood samples were centrifuged at 2000 *g* for 10 min and the plasma pipetted into sample tubes, which were stored at -20° C until processing in a single batch. All urine was collected in a container from 10.00 h to 22.00 h, after voiding the bladder at 10.00 h.

Nociceptive tests

During all nociceptive tests the subjects were in a comfortable position in a quiet and warm room without distractions. All tests were conducted by the same investigator, who was blind to the randomization sequence of study medication. The tests were conducted in the sequence shown below, at the start of the study and 1.5, 3.3, 5 and 10 h after the dihydrocodeine or placebo dose.

Heat pain test Heat pain tolerance tests were performed using the Pain 2 programme of the Pathtester MPI100 (Phywe Instruments, Göttingen, Germany), which is a thermal stimulator system based on a computer-controlled peltier element [12]. The peltier element has a size of 1.5×3.5 cm and was placed on the thenar eminence of the dominant hand with standardized pressure. In the Pain 2 programme the subject is instructed to titrate the point of maximum pain tolerance by increasing or decreasing the temperature of the peltier element at a fixed rate of 0.7° C/second. Once the pain tolerance threshold is reached, this temperature is maintained for 10 s and the subject can then fine tune to the threshold, if necessary. The mean of five successive test runs is recorded. This form of test excludes reaction time differences and allows good titration of thresholds. A maximum stimulation temperature of 52° C was used to prevent tissue damage.

Electrical threshold tests First sensation and pain tolerance thresholds were tested on the thenar eminence of the nondominant hand using a nerve stimulator (Digistim 3 plus, Organon Teknika) [13]. The position of the electrodes was marked on the skin to ensure precise placement and skin resistance was minimized. Stimulation was with 100Hz and constant current was increased at a rate of 0.1 mA per second. A maximum stimulation current of 20 mA to prevent tissue damage.

Rectal distension thresholds A well-lubricated latex balloon was atraumatically advanced 5 cm into the rectum with the subjects in a relaxed left lateral position on a bed. The balloon was prepared in standardized fashion by tying a latex preservative over the end of a soft plastic catheter of 5 mm external diameter, identically to those used clinically for anorectal physiology by our Gastrointestinal Unit [14]. The compliance of these balloons is close to infinite at volumes below 700 ml. Each balloon was only used once. The balloon was inflated at a rate of 10 ml per second and three thresholds documented: first sensation, rectal defaecatory urge and distension pain tolerance. Two successive distension runs were performed, the second was used for analyses. The maximum distension allowed was 700 ml.

Dihydrocodeine and dihydromorphine analysis in plasma

Determination of free and enzymatically hydrolysed plasma dihydrocodeine and dihydromorphine was performed by the Dr Margarete Fischer-Bosch-Institut für Klinische Pharmakologie in Stuttgart with gas chromatography – tandem mass spectrometry and detection limits were 2 ng ml^{-1} (6.6 nmol ml^{-1}) and 40 pg ml^{-1} (139 pmol ml^{-1}), respectively, as previously published [15]. The inter-day coefficient of variability was below 20% for both compounds. Enzymatic hydrolysis was performed with E. coli glucuronidases, with a hydrolysis efficacy for dihydrocodeine-6-glucuronide of 53–63%.

Urine samples

Quantification of the excreted metabolites in the 12 h urine was performed by micellar electrokinetic capillary chromatography, as previously reported [16]. The results of the urinary analysis have been reported separately [17]. The

detection limits were 30 ng ml^{-1} for dihydrocodeine and 50 ng ml^{-1} for dihydromorphine, nordihydromorphine, nordihydrocodeine and dihydrocodeine glucuronide. The interday coefficient of variability was below 5% for all metabolites.

Statistics

Analysis of variance (ANOVA) was performed for the plasma metabolite concentrations using the STATISTICA 5.1 (1997) analysis software, as these were normally distributed and continuous data. These data are expressed as means and 95% confidence intervals. Non-normally distributed or discontinuous variables, such as the pain thresholds, were analysed for each sampling point using Kruskal-Wallis ANOVA followed by Mann–Whitney-*U*-testing. These data are shown as medians and 95% confidence intervals. Additionally, to assess the significance of the results, the 95% confidence intervals of the area-under-the-curve (AUC) values for the key difference between the quinidine (quinidine with dihydrocodeine minus quinidine with placebo) and placebo (placebo with dihydrocodeine minus placebo with placebo) treatments were calculated. For plasma concentrations the 95% CI ranges of the differences in AUC of dihydrocodeine and dihydromorphine with and without quinidine were calculated and compared.

If volunteers' thresholds exceeded the maximum allowed stimulation, their data could not be evaluated for that specific test, as no accurate change from baseline or differences between groups could be calculated. A significance threshold of $P<0.05$ was used.

Results

A total of 11 volunteers were recruited for the study. Ten completed the entire study and no side-effects were reported. One volunteer tested as a poor metabolizer of debrisoquine and was therefore replaced before the beginning of the study.

Phasic electrical skin thresholds

Eight subjects were completely evaluable, as two could not be analysed because their pain tolerance thresholds were higher than the maximum stimulation intensity allowed in the study design. The differences in the thresholds for first sensation or pain tolerance (Figure 1) between all of the study groups were not significant (Table 1 for 95% confidence intervals of comparison).

Tonic heat pain tolerance thresholds

One subject was excluded from this analysis, as his heat pain tolerance was higher than the maximum stimulation temperature allowed. Dihydrocodeine raised heat pain thresholds significantly compared with placebo at 3.3 h and 5 h postdosing (Figure 2) ($P<0.05$). Quinidine had no significant effect on thresholds compared with placebo at any time (Table 1). Premedication with quinidine did not significantly alter the increased thresholds measured with dihydrocodeine (Table 1).

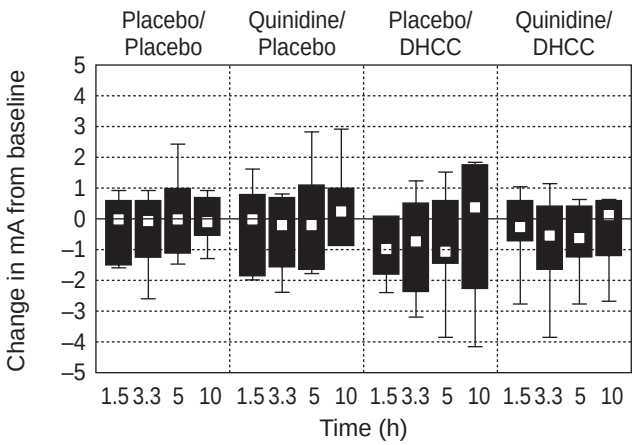

Figure 1 Box-whisker plots of changes in phasic electrical pain thresholds in eight healthy volunteers following single doses of placebo with placebo, quinidine 50 mg with placebo, placebo with slow-release dihydrocodeine 60 mg (DHCC) and quinidine 50 mg with slow-release dihydrocodeine 60 mg. The medians are represented by symbols, the 95% confidence intervals by boxes and the minimum and maximum values by whiskers. There were no significant group differences. 95% confidence intervals for differences in Table 1.

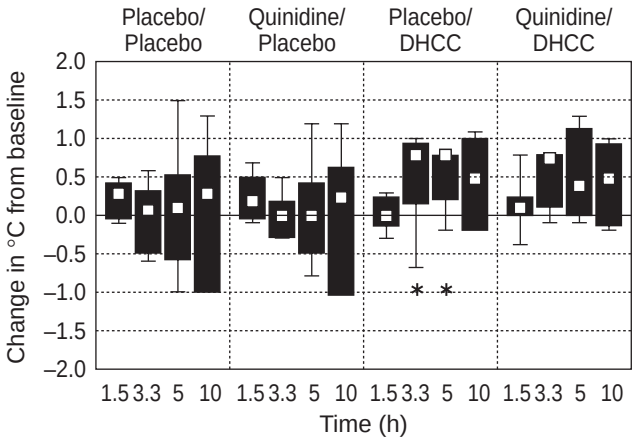

Figure 2 Box-whisker plots of changes in tonic heat pain thresholds in nine healthy volunteers following single doses of placebo with placebo, quinidine 50 mg with placebo, placebo with slow-release dihydrocodeine 60 mg (DHCC) and quinidine 50 mg with slow-release dihydrocodeine 60 mg. The medians are represented by symbols, the 95% confidence intervals by boxes and the minimum and maximum values by whiskers. The thresholds were significantly higher following placebo with dihydrocodeine than after placebo with placebo at 3.3 h and 5 h ($*P<0.05$), but there were no differences compared with quinidine with dihydrocodeine. 95% confidence intervals for differences in Table 1.

Rectal distension thresholds

Nine subjects were available for complete analysis. One subject was excluded, as his rectal distension thresholds were markedly below our normal values [13]. This was due to a narrow and low-compliance rectum. Quinidine alone did not change the first sensation, defaecatory urge and pain tolerance thresholds (Figures 3 and 4). Dihydrocodeine

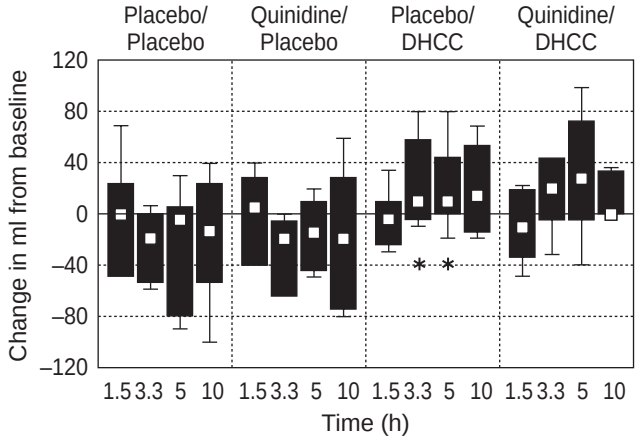

Figure 3 Box-whisker plots of changes in rectal distension pain thresholds in nine healthy volunteers following single doses of placebo with placebo, quinidine 50 mg with placebo, placebo with slow-release dihydrocodeine 60 mg (DHCC) and quinidine 50 mg with slow-release dihydrocodeine 60 mg. The medians are represented by symbols, the 95% confidence intervals by boxes and the minimum and maximum values by whiskers. The thresholds were significantly higher following placebo with dihydrocodeine than after placebo with placebo at 3.3 h and 5 h ($^{\star}P<0.05$), but there were no differences compared with quinidine with dihydrocodeine. 95% confidence intervals for differences in Table 1.

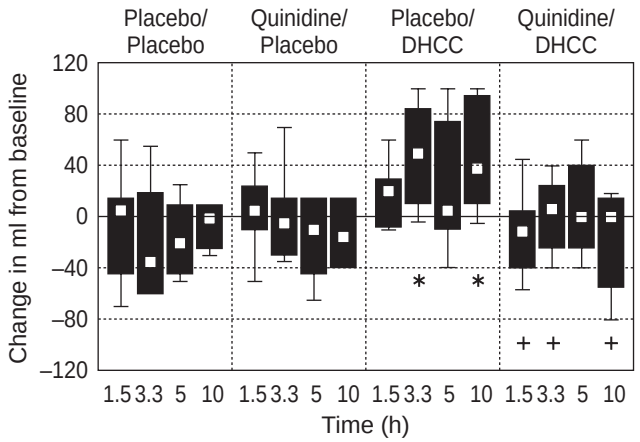

Figure 4 Box-whisker plots of changes in rectal distension defaecatory urge thresholds in nine healthy volunteers following single doses of placebo with placebo, quinidine 50 mg with placebo, placebo with slow-release dihydrocodeine 60 mg (DHCC) and quinidine 50 mg with slow-release dihydrocodeine 60 mg. The medians are represented by symbols, the 95% confidence intervals by boxes and the minimum and maximum values by whiskers. The thresholds were significantly higher following placebo with dihydrocodeine than after placebo with placebo at 3.3 h and 10 h ($^{\star}P<0.02$). The addition of quinidine to dihydrocodeine significantly lowered urge thresholds compared with placebo with dihydrocodeine at 1.5 h, 3.3 h and 10 h ($^{+}P<0.05$).

dosing significantly elevated the defaecatory urge (at 3.3 h and 10 h postdosing, $P<0.02$) and pain tolerance thresholds (at 3.3 h and 5 h postdosing, $P<0.05$) (Figures 3 and 4), but first sensation thresholds were unchanged (Table 1). Premedication with quinidine did not significantly modify the effects of dihydrocodeine on first sensation and pain tolerance thresholds (Figure 3). However, the defaecatory urge thresholds were decreased by the addition of quinidine to dihydrocodeine at 1.5 h, 3.3 h and 10 h postdosing ($P<0.05$) (Figure 4).

Plasma dihydrocodeine and dihydromorphine

All data from the 10 volunteers were evaluable. The free and hydrolysed plasma dihydromorphine concentrations were significantly reduced with quinidine premedication compared with placebo at all measurement times (all $P<0.005$), but dihydrocodeine levels were unchanged (Tables 1 and 2).

Urinary dihydrocodeine metabolite excretion

Data from all 10 subjects were complete. The median percentage of the dihydrocodeine dose excreted as dihydromorphine after hydrolysis and extraction was 0.91% (95% confidence interval: 0.60–1.42) without quinidine and 0.28% (95% confidence interval: 0.18–0.48) with quinidine pretreatment (Figure 5, Table 1) ($P<0.001$).

Discussion

The aim of this study was to assess whether dihydromorphine plays a significant role in dihydrocodeine-induced analgesia. For this purpose quinidine was used to convert extensive metabolizers of dihydrocodeine to dihydromorphine to poor metabolizers, hereby reducing the production of dihydromorphine significantly. The use of quinidine in doses of 50 mg and higher to induce the poor metaboliser state by blocking the cytochrome P450 2D6 (CYP 2D6) pathway is well-validated [6, 10, 18–20]. This study showed a single dose of sustained-release dihydrocodeine alone significantly raised the tonic heat pain tolerance, the rectal distension defaecatory urge and rectal distension pain tolerance thresholds compared to placebo in healthy volunteers. Blockade of the CYP 2D6-dependent metabolism of dihydrocodeine to dihydromorphine with quinidine premedication did not significantly change pain tolerance thresholds, although plasma concentrations and urinary excretion of dihydromorphine were significantly reduced. Only very low concentrations of dihydromorphine were available systemically and only 0.91% of the dihydrocodeine dose was excreted as dihydromorphine in extensive metabolizers and 0.28% in quinidine-induced poor metabolizers. In the present study free and hydrolysed dihydromorphine metabolite concentrations were measured and consequently a differentiation of the glucuronides and other metabolites was not possible.

The conversion of dihydrocodeine to dihydromorphine and also of codeine to morphine via the CYP 2D6 pathway is diminished in $\approx$5–10% of Caucasians due to genetic polymorphism [9]. As both dihydromorphine and morphine are potent analgesics, it has been postulated that poor metabolizers of dihydrocodeine and codeine will derive less analgesic effect [4–7]. The effect of reduced *O*-demethylation of codeine on metabolite formation and on analgesia has been previously studied. The blockade by quinidine of the metabolism of codeine to morphine and to the analgesically potent morphine-6-glucuronide and normorphine did not consistently reduce pain thresholds [6, 21].

Table 1 Differences in 95% confidence intervals for AUCs between treatment groups.

Thresholds	*95% confidence intervals of (Quinidine and DHCC—Quinidine and Placebo) minus (Placebo and DHCC–Placebo and Placebo)*
Electrical sensation	−0.8–2.1
Electrical pain tolerance	−1.9–1.7
Heat pain tolerance	−2.0–4.2
Rectal sensation	−105–45
Rectal defaecatory urge	−732––5
Rectal pain tolerance	−205–103
Metabolites	*95% confidence intervals of (Placebo and DHCC—Quinidine and DHCC)*
Dihydrocodeine free	−362–889
Dihydromorphine free	20–55
Dihydrocodeine hydrolysed	−4844–1517
Dihydromorphine hydrolysed	190–453
% of dihydrocodeine dose excreted in urine as dihydromorphine	0.43–0.74

DHCC = dihydrocodeine.

Table 2 Plasma dihydrocodeine and dihydromorphine concentrations (means and 95% confidence intervals) after dihydrocodeine with placebo or quinidine pretreatment. The free (a) and hydrolysed (b) plasma concentrations in nM are listed. ⋆$P<0.005$ placebo *vs* quinidine pretreatment.

a Free	*0 h*	*1.5 h*	*3.3 h*	*5 h*	*10 h*	*13.5 h*
			Placebo pretreatment and dihydrocodeine			
Dihydrocodeine	0.0	232 (178–286)	424 (297–552)	400 (311–488)	236 (163–309)	125 (97–153)
Dihydromorphine	0.0	2.9⋆ (1.2–4.7)	5.3⋆ (2.4–8.1)	4.0⋆ (2.3–5.8)	2.9⋆ (1.8–3.9)	1.8⋆ (1.1–2.5)
			Quinidine pretreatment and dihydrocodeine			
Dihydrocodeine	0.0	245 (204–286)	374 (285–463)	323 (259–386)	189 (144–234)	101 (78–124)
Dihydromorphine	0.0	0.7⋆ (0.5–0.9)	1.3⋆ (0.8–1.9)	1.1⋆ (0.7–1.5)	0.8⋆ (0.5–1.1)	0.6⋆ (0.3–0.8)
b Hydrolysed						
			Placebo pretreatment and dihydrocodeine			
Dihydrocodeine	0.0	650 (468–831)	1512 (866–2158)	1445 (1088–1803)	842 (716–968)	561 (426–695)
Dihydromorphine	0.0	19.6⋆ (11.0–28.3)	40.7⋆ (22.5–59.0)	49.3⋆ (30.2–68.5)	39.1⋆ (21.4–56.7)	28.0⋆ (15.9–40.0)
			Quinidine pretreatment and dihydrocodeine			
Dihydrocodeine	0.0	936 (561–1310)	2149 (541–3758)	1634 (1168–2105)	928 (543–1314)	693 (439–768)
Dihydromorphine	0.0	6.5⋆ (4.6–8.6)	12.9⋆ (9.3–16.5)	15.1⋆ (11.0–19.2)	11.5⋆ (8.1–15.0)	7.9⋆ (5.3–10.4)

This may be due to methodological factors, such as insufficiently sensitive stimulation procedures, or to a direct analgesic effect of codeine itself. The urinary excretion of morphine was 3–6% of the codeine dose in extensive metabolizers and ≈0.33% in poor metabolizers, of which 0.001% was unconjugated morphine [8, 9, 22]. The role of morphine metabolites in dihydrocodeine-related analgesia is likely to be even less significant, as the percentage of dihydrocodeine excreted as dihydromorphine diminished from only 0.91% in extensive metabolizers to 0.28% in poor metabolizers. This coincided with 3–4-fold lower dihydromorphine plasma concentrations in quinidine-induced poor metabolizers compared with extensive metabolizers (see Table 2).

It has been hypothesized that there is cerebral production of morphine metabolites from codeine and dihydrocodeine and that quinidine does not cross the blood brain barrier [23]. Furthermore, CYP 2D6 enzyme has been demonstrated in animal brain tissue [24]. Consequently, plasma metabolite concentrations, reflecting only the systemic biophase, and extracerebral quinidine blockade of CYP 2D6 would clearly not permit conclusions concerning the action of cerebral

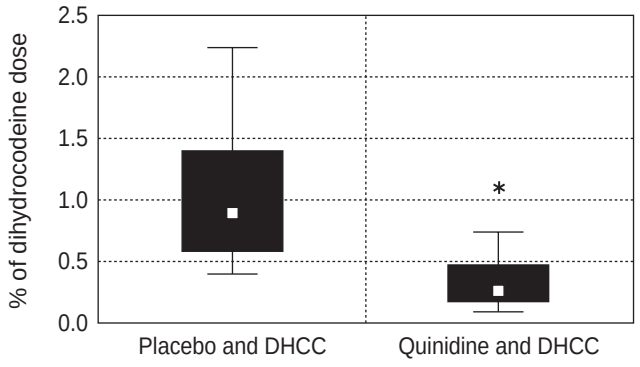

Figure 5 Box-whisker plots of the percentage of the dihydrocodeine dose recovered as dihydromorphine in the 12 h urine of 10 healthy volunteers following single doses of slow-release dihydrocodeine 60 mg with placebo and slow-release dihydrocodeine 60 mg with quinidine 50 mg. The medians are represented by symbols, the 95% confidence intervals by boxes and the minimum and maximum values by whiskers. The excreted urinary dihydromorphine was significantly diminished by quinidine premedication (*$P<0.001$).

metabolites. Quinidine would not effectively induce the poor metabolizer state. However, quinidine has recently been shown to penetrate the blood–brain barrier in measurable quantities and morphine concentrations in both cerebrospinal fluid and plasma following an oral dose of codeine were significantly depressed after quinidine premedication [25]. The importance of a potential analgesic contribution of cerebrally formed morphine metabolites remains open, but it appears quinidine can also inhibit central CYP 2D6. Quinidine alone did not significantly decrease pain thresholds with dihydrocodeine in our study or in a previous study with codeine [21].

The effects of dihydrocodeine on both somatic and visceral sensation and pain tolerance thresholds were assessed. The differential effects of opioids on phasic and tonic thresholds have been previously described [26, 27]. Opioids do not appear to modulate sensation or phasic pain thresholds, but increase pain tolerance or C-fibre related thresholds. This was confirmed in the present study with dihydrocodeine, where skin and visceral sensation thresholds, as well as phasic electrical pain tolerance thresholds were not affected. However, tonic heat pain and visceral pain tolerance thresholds were consistently raised for up to 10 h after dosing.

The rectal stimulation tests were performed with a standardized latex preservative tied to a flexible catheter. This technique is well validated in our research unit and normal values are available [14]. The intraindividual cross-over comparison using a standardized protocol will compensate for interindividual differences in rectal compliance, although changes in rectal tone due to the study drugs could not be directly assessed. However, the raised distension urge and pain thresholds observed with dihydrocodeine cannot be primarily attributed to changes in compliance or tone as the sensation thresholds were not affected.

The increased defaecatory urge thresholds secondary to dihydrocodeine may be one of the mechanisms involved in opioid-related constipation, besides the wellknown motility changes. By delaying the call to defaecation rectal emptying will be postponed, with possible hardening of faeces and more forceful expulsion. The inhibition of the raised defaecatory urge threshold by the addition of quinidine to dihydrocodeine is unexplained, but the morphine metabolite may be implicated.

In conclusion, quinidine did not significantly attenuate the antinociceptive effects of a single dose of dihydrocodeine. These results imply the systemic morphine metabolites of dihydrocodeine are not of major importance for the analgesic effect of dihydrocodeine and that poor metabolizers could derive similar analgesia as extensive metabolizers. However, confirmation of these results with repeated dosing is necessary.

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References

1 Keats AS, Telford J, Kuruso Y. Side action of dihydrocodeine. *J Pharmacol Exp Ther* 1957; **119**: 155–160.
2 Seed JC, Wallenstein SL, Houde RW, Bellville JW. A comparison of the analgesic and respiratory effects of dihydrocodeine and morphine in man. *Arch Int Pharmacodyn Ther* 1958; **116**: 293–339.
3 Cass LJ, Frederick WS. An experimental and statistical method in the study of new drugs. *Arch Int Med* 1958; **102**: 571–580.
4 Sanfilippo G. Contributo sperimentale all'ipotesi della smetilazione della codeine nell organismo. *Boll Soc Ital Biol Sper* 1948; **24**: 723–726.
5 Sindrup SH, Brøsen K, Bjerring P, *et al*. Codeine increases pain thresholds to copper vapor laser stimul in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1990; **49**: 686–693.
6 Desmeules J, Gascon MP, Dayer P, Magistris M. Impact of environmental and genetic factors on codeine analgesia. *Eur J Clin Pharmacol* 1991; **41**: 23–26.
7 Mikus G, Somogyi AA, Bochner F, Chen ZR. Polymorphic metabolism of opioid narcotic drugs: possible clinical implications. *Ann Acad Med Singapore* 1991; **20**: 9–12.
8 Yue QY, Hasselstrøm J, Svensson JO, Säwe J. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1991; **31**: 635–642.
9 Yue QY, Säwe J. Interindividual and interethnic differences in codeine metabolism. In *Pharmacogenetics of drug metabolism*, ed Kalow K. Pergamon Press, New York, 1992, p. 721–727.
10 Speirs CJ, Murray S, Boobis AR, Seddon CE, Davies DS. Quinidine and the identification of drugs whose elimination is impaired in subjects classified as poor metabolisers of debrisoquine. *Br J Clin Pharmacol* 1986; **22**: 739–743.
11 Küpfer A, Preisig R. Mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol* 1984; **26**: 753–759.
12 Lautenbacher S, Rollman GB. Sex differences in responsiveness to painful and non-painful stimuli are dependent upon stimulation method. *Pain* 1993; **53**: 255–264.
13 Wilder-Smith OHG, Tassonyi E, Senly C, Otten P. Arendt-Nielsen l. Surgical pain is followed not only by spinal

sensitisation, but also by supraspinal antinociception. *Br J Anaesth* 1996; **76**: 816–821.
14 Wilder-Smith CH. Viscerocutaneous nociception and anorectal motor function: a prospective study in asymptomatic, healthy volunteers. *Gastroenterol* 1995; **108**: A709.
15 Hofmann U, Fromm MF, Johnson S, Mikus G. Simultaneous determination of dihydrocodeine and dihydromorphine in plasma by gas chromatography—tandem mass spectrometry. *J Chromatogr B* 1995; **663**: 59–65.
16 Hufschmid E, Theurillat R, Martin U, Thormann W. Exploration of the metabolism of dihydrocodeine via determination of its metabolites in human urine using micellar electrokinetic capillary chromatography. *J Chromatogr B* 1995; **668**: 159–170.
17 Hufschmid E, Theurillat R, Wilder-Smith CH, Thormann W. Characterization of the genetic polymorphism of dihydrocodeine O-demethylation in man via analysis of urinary dihydrocodeine and dihydromorphine by micellar electrokinetic capillary chromatography. *J Chromatogr B* 1996; **678**: 43–51.
18 Leeman T, Dayer P, Meyer UA. Single-dose quinidine treatment inhibits metoprolol oxidation in extensive metabolizers. *Eur J Clin Pharmacol* 1986; **29**: 739–741.
19 Brinn R, Brøsen K, Gram LF, Haghfelt T, Otton SV. Sparteine oxidation is practically abolished in quinidine-treated patients. *Br J Clin Pharmacol* 1986; **22**: 194–197.
20 Brøsen K, Gram LF, Haghfelt T, Bertilsson L. Extensive metabolizers of debrisoquine become poor metabolizers during quinidine treatment. *Pharmacol Toxicol* 1987; **60**: 312–314.
21 Sindrup SH, Arendt-Nielsen L, Brøsen K, Bjerring P, Angelo HR, Eriksen B, Gram LF. The effect of quinidine on the analgesic effect of codeine. *Eur J Clin Pharmacol* 1992; **42**: 587–592.
22 Persson K, Hammarlund-Udenaes M, Mortimer O, Rane A. The postoperative pharmacokinetics of codeine. *Eur J Clin Pharmacol* 1992; **42**: 663–666.
23 Chen ZR, Irvine RJ, Bochner F, Somogyi AA. Morphine formation from codeine in the rat brain: a possible mechanism of codeine analgesia. *Life Sci* 1990; **46**: 1067–1074.
24 Niznik HB, Tyndale RF, Sallee FR, *et al*.The dopamine transporter and cytochrome P450IIDI in brain. *Arch Biochem Biophys* 1990; **276**: 424–432.
25 Sindrup SH, Hofmann U, Asmussen J, *et al*. Impact of quinidine on plasma and cerebrospinal fluid concentrations of codeine and morphine after codeine intake. *Eur J Clin Pharmacol* 1996; **49**: 503–509.
26 Van den Burght M, Rasmussen SE, Arendt-Nielsen L, Bjerring P. Morphine does not affect laser-induced warmth and pinprick thresholds. *Acta Anaesthesiol Scand* 1994; **38**: 161–164.
27 Le Bars D. Guilbaud G. Jurna I. Besson JM. Opioid effects on nerve transmission. *Brain Res* 1976; **115**: 518–524.

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